

## Breast cancer in systemic lupus

Bernatsky, S; Ramsey-Goldman, R; Petri, M; Urowitz, M B; Gladman, D D; Fortin, P F; Ginzler, E; Romero-Diaz, J; Peschken, C; Jacobsen, S; Hanly, J G; Nived, O; Yelin, E H; Isenberg, D; Rahman, A; Bae, S-C; Joseph, L; Witte, T; Ruiz-Irastorza, G; Aranow, C

DOI:

[10.1177/0961203316664595](https://doi.org/10.1177/0961203316664595)

License:

None: All rights reserved

*Document Version*

Peer reviewed version

*Citation for published version (Harvard):*

Bernatsky, S, Ramsey-Goldman, R, Petri, M, Urowitz, MB, Gladman, DD, Fortin, PF, Ginzler, E, Romero-Diaz, J, Peschken, C, Jacobsen, S, Hanly, JG, Nived, O, Yelin, EH, Isenberg, D, Rahman, A, Bae, S-C, Joseph, L, Witte, T, Ruiz-Irastorza, G, Aranow, C, Kamen, D, Sturfeldt, G, Foulkes, WD, Hansen, JE, St Pierre, Y, Raymer, PC, Tessier-Cloutier, B, Clarke, AE & Gordon, C 2017, 'Breast cancer in systemic lupus', *Lupus*, vol. 26, no. 3, pp. 311-315. <https://doi.org/10.1177/0961203316664595>

[Link to publication on Research at Birmingham portal](#)

### **Publisher Rights Statement:**

(c) Sage 2016. Final Version of record available at: <https://doi.org/10.1177/0961203316664595>

### **General rights**

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

### **Take down policy**

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact [UBIRA@lists.bham.ac.uk](mailto:UBIRA@lists.bham.ac.uk) providing details and we will remove access to the work immediately and investigate.

## Breast cancer in systemic lupus

**Sasha Bernatsky<sup>1,2</sup>, Rosalind Ramsey-Goldman<sup>3</sup>, Michelle Petri<sup>4</sup>, Murray B. Urowitz<sup>5</sup>, Dafna D. Gladman<sup>5</sup>, Paul F. Fortin<sup>6</sup>, Ellen Ginzler<sup>7</sup>, Juanita Romero-Diaz<sup>8</sup>, Christine Peschken<sup>9</sup>, Soren Jacobsen<sup>10</sup>, John G. Hanly<sup>11</sup>, Caroline Gordon<sup>12</sup>, Ola Nived<sup>13</sup>, Edward H. Yelin<sup>14</sup>, David Isenberg<sup>15</sup>, Anisur Rahman<sup>15</sup>, Sang-Cheol Bae<sup>16</sup>, Lawrence Joseph<sup>1,2</sup>, Torsten Witte<sup>17</sup>, Guillermo Ruiz-Irastorza<sup>18</sup>, Cynthia Aranow<sup>19</sup>, Diane Kamen<sup>20</sup>, Gunnar Sturfeldt<sup>13</sup>, William D. Foulkes<sup>21</sup>, James E. Hansen<sup>22</sup>, Yvan St. Pierre<sup>2</sup>, Patrice Chrétien Raymer<sup>2</sup>, Basile Tessier-Cloutier<sup>23</sup>, Ann E. Clarke<sup>24</sup>**

<sup>1</sup> Faculty of Medicine, McGill University, Montreal, Quebec, Canada

<sup>2</sup> Division of Clinical Epidemiology, Research Institute of the McGill University Health Centre, Montreal, Quebec, Canada

<sup>3</sup> Feinberg School of Medicine, Northwestern University, Chicago, Illinois, USA

<sup>4</sup> Division of Rheumatology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA.

<sup>5</sup> Centre for Prognosis Studies in the Rheumatic Diseases, Toronto Western Hospital and University of Toronto, Toronto, Ontario, Canada.

<sup>6</sup> Division of Rheumatology, Centre de recherche du CHU de Québec - Université Laval, Quebec City, Canada.

<sup>7</sup> State University of New York–Downstate Medical Center, Brooklyn; New York, USA

<sup>8</sup> Instituto Nacional de Ciencias Medicas y Nutrición, Mexico City, Mexico.

<sup>9</sup> University of Manitoba, Winnipeg, Manitoba, Canada.

<sup>10</sup> Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark

<sup>11</sup> Division of Rheumatology, Dalhousie University and Nova Scotia Health Authority, Halifax, Nova Scotia, Canada.

<sup>12</sup> Rheumatology Research Group, Institute for Inflammation and Ageing,, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK; Rheumatology department, City Hospital, Sandwell and West Birmingham Hospitals NHS Trust and NIHR/Wellcome Trust Clinical Research Facility, Queen Elizabeth Hospital Birmingham, University Hospital Birmingham NHS Foundation Trust, Birmingham, UK

<sup>13</sup> Department of Rheumatology, Institution of Clinical Sciences, Lund University Hospital, Lund, Sweden.

<sup>14</sup> Department of Medicine , University of California, San Francisco, California, USA

<sup>15</sup> Centre for Rheumatology Research, University College London, London, UK.

<sup>16</sup> The Hospital for Rheumatic Diseases, Hanyang University, Seoul, Korea

<sup>17</sup> Department of Clinical Immunology, Hannover Medical School, Hannover, Germany.

<sup>18</sup> Autoimmune Diseases Research Unit, Department Of Internal Medicine, Hospital Universitario Cruces, University Of The Basque Country, Bizkaia, The Basque Country, Spain.

<sup>19</sup> Feinstein Institute for Medical Research, Manhasset, New York, New York.

<sup>20</sup> Division of Rheumatology and Immunology, Medical University of South Carolina, Charleston, South Carolina, USA.

<sup>21</sup> Departments of Oncology, Human Genetics and Medicine, McGill University, Montreal, Quebec, Canada

<sup>22</sup> Department of Therapeutic Radiology, Yale School of Medicine, New Haven, Connecticut. USA

<sup>23</sup> Department of Anatomical Pathology, University of British Columbia, Vancouver, BC, Canada.

<sup>24</sup> Division of Rheumatology, University of Calgary, Alberta, Canada.

## **ABSTRACT**

**Objective:** There is a decreased breast cancer risk in SLE versus the general population. We assessed a large sample of SLE patients, evaluating demographic and clinical characteristics and breast cancer risk.

**Methods:** We performed case-cohort analyses within a multi-centre international SLE sample. We calculated the breast cancer hazard ratio (HR) in female SLE patients, relative to demographics, reproductive history, family history of breast cancer, and time-dependent measures of anti-dsDNA positivity, cumulative disease activity, and drugs, adjusted for SLE duration.

**Results:** There were 86 SLE breast cancers and 4,498 female SLE cancer-free controls. Patients were followed on average for 7.6 years. Versus controls, SLE breast cancer cases tended to be white and older. Breast cancer cases were similar to controls regarding anti-dsDNA positivity, disease activity and most drug exposures over time. In univariate and multivariate models, the principal factor associated with breast cancers was older age at cohort entry.

**Conclusions:** There was little evidence that breast cancer risk in this SLE sample was strongly driven by any of the clinical factors that we studied. Further search for factors that determine the lower risk of breast cancer in SLE may be warranted.

**Abstract word count: 190**

**Manuscript word count: 2,705**

**Key words:** Breast cancer, systemic lupus erythematosus

## Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by widespread inflammation leading to a multitude of manifestations in skin, joints, kidneys, and other organs. In SLE, there appears to be about an overall 15% increase in cancer but a decrease in certain cancers. [1] Specifically, the standardized incidence ratio (or relative rate) for breast cancer in SLE has been estimated in a meta-analysis to be 0.76 (95% confidence interval, CI 0.69-0.85) when compared to age and sex matched general population controls. [2] Many theories have arisen in an attempt to explain this phenomenon, such as hypotheses that breast cancer risk in SLE may be reduced by drug exposures (non-steroidal anti-inflammatory drugs, NSAIDs, anti-malarial drugs, etc) or autoantibody profiles, but no data have evaluated these hypotheses.

Our primary objective was thus to assess breast cancer risk in females with SLE, comparing patients in terms of demographic and clinical factors.

## Methods:

We used data from a very large multi-site international SLE cohort (30 centres, 16,409 patients), with the participation of collaborating centres from two research networks, the Systemic Lupus International Collaborating Clinics (SLICC) and the Canadian Network for Improved Outcomes in Systemic Lupus, as well as other collaborators [3] The patients, who either fulfill the 1997 American College of Rheumatology (ACR) classification criteria for SLE [4] or have a clinical diagnosis of SLE made by a rheumatologist, are enrolled in clinical cohort registries and followed by specialists.

The case-cohort design is a well-described variant of the standard case-control study, which optimizes flexibility and efficiency. In this design, a random subset is chosen from the baseline patients (who are all free of the event of interest) and that subset is the source of controls over time. At each cancer ‘event’ that occurs over time, the case is compared to the cancer-free controls remaining in that subset sample, on the exposures and variables of interest. The statistical analysis is a modified hazard regression. [5]

Although all centres who participated in our very large cohort study collect data on demographics, 18 centres provided the data required for a case-cohort analysis. The data was not uniformly available on all patients across the 18 cohorts; in some cases, the centres had to perform chart review to obtain the necessary variables. This made the case-cohort approach more feasible than a simple cohort analysis. Thus, the data presented in this analysis are from these centres: Halifax, Montreal, Toronto, Winnipeg, (all in Canada), Baltimore, Chicago, San Francisco Bay Area, Albert

Einstein, New York City – State University of New York, South Carolina, (all in the United States), Copenhagen (Denmark), London and Birmingham (England), Bizkaia (Spain), Seoul (South Korea), Hannover (Germany), Lund (Sweden), and Mexico City (Mexico).

We studied only breast cancer cases that had occurred after entry into the lupus cohort at each centre and up to the time of cohort exit (defined by death or date of last visit). The index time for each risk (case-control) set was the date of the case's breast cancer occurrence, with time since SLE diagnosis as the time axis. The controls for each risk set, for each breast cancer case, represented all the subcohort members who remained cancer-free up to that index time. Subjects who developed a cancer other than breast cancer were right-censored.

We used the modified Cox proportional hazards regression case-cohort analyses to calculate the hazard ratio (HR) for breast cancer risk in female SLE patients. We included in our model a time-dependent measure, the mean adjusted SLE disease activity, based on SLE Disease Activity Index (SLEDAI-2K) scores over time.[6] We were also interested specifically in autoantibody profiles, so for our analyses we removed the item for anti-dsDNA from the SLEDAI scores and constructed a separate variable for this. To produce 'mean adjusted SLEDAI-2K' scores over time we used the previously published approach [7] of calculating areas under the curve for SLEDAI-2K values from time zero to the event time of each risk set. The area under the curve is then divided by the time over which activity has been measured (this time is the same for all members of a risk set) and this produces a mean adjusted SLEDAI-2K, which has the same units as the original SLEDAI-2K measure. The mean adjusted SLEDAI-2K scores for each member of each risk set was categorized into quartiles, and in our primary analyses, our variable captured the effect of being in the highest quartile of mean adjusted SLEDAI-2K (versus lower disease activity). At one centre (San Francisco), disease activity was captured only with self-report items of disease activity, as opposed to the standard physician-scored SLEDAI-2K, using a measure validated against the SLEDAI.[8] We performed sensitivity analyses with and without this centre and results were essentially unchanged, hence the primary results reported in this paper included all centres.

As mentioned, we also evaluated anti-dsDNA positivity, using a weighted average of the number of times patients were anti-dsDNA antibody positive over time. The dsDNA antibody test information that we relied on was based on the ACR classification criterion for dsDNA antibody positivity at cohort enrolment, as well as the SLEDAI-2K disease activity item for this test. The dsDNA antibody testing was done locally at each centre with variable assays.

The data on demographics (age at cohort entry, as a continuous time-dependent variable, and race/ethnicity), disease activity over time, and all medications of interest, were prospectively recorded in the clinic database and/or medical records at each centre. Medications were included as time-dependent variables for ever-never use, for all the medications listed in Table 2. We included cumulative exposures for systemic steroids, azathioprine, cyclophosphamide, and anti-malarial agents, in our full multivariate model. These variables, calculated from the most detailed records available, used cut-offs as previously described<sup>9</sup>. We also included variables for menopausal status, family history of breast cancer, and number of pregnancies. As time zero for the observation interval was SLE diagnosis, our analyses also adjusted for SLE duration, and we adjusted for calendar year. We included one set of analyses where we stratified results by centre in order to account for the possibility of differences across centres. Both the stratified and non-stratified multivariable models were adjusted for all demographic and clinical variables in the model.

## Results:

We analyzed 86 SLE breast cancer cases and 4,498 female SLE controls. Patients had been followed an average of 7.6 (standard deviation 6.9) years. In the descriptive analyses, compared to controls, SLE breast cancer cases tended to be older at cohort entry (Table 1) and white (possibly reflecting racial/ethnic variations in breast cancer risk in the general population) [10]. Breast cancer cases were similar to controls regarding baseline disease activity. A similar proportion of cases and cancer-free controls were anti-dsDNA positive at cohort entry, and through the observation interval.

In univariate and multivariate models (Table 2), the principal demographic factor associated with breast cancer was older age at cohort entry. In univariate analyses only, white race/ethnicity, hormone replacement therapy, menopausal status, and family history of breast cancer were positively associated with breast cancer; these associations were imprecise in the multivariate analyses. For most of the drug exposures, the HR confidence intervals were wide. A negative correlation between cumulative azathioprine and breast cancer was suggested in univariate analyses but in the multivariate analyses the HR was close to the null value. We could not detect a clear association of breast cancer risk with SLE disease activity (excluding dsDNA positivity) or anti-dsDNA positivity over time.

## DISCUSSION:

As mentioned in the introduction, previous data clearly point towards a decreased risk of breast cancer in SLE. [2,3,11] Many theories have arisen in an attempt to explain this phenomenon, such as

hypotheses that breast cancer risk in SLE may be reduced by drug exposures (non-steroidal anti-inflammatory drugs, NSAIDs, anti-malarial drugs, etc) or autoantibody profiles, but our study is the first to explore these hypotheses.

In fact, our novel study is one of only a handful of investigations focussing on breast cancer risk in SLE. One previous study relied on administrative data from the United States, which studied only elderly patients without clinically confirming their diagnosis of SLE<sup>12</sup>. That study showed a decreased risk for estrogen receptor-negative breast cancer, but was unable to examine clinical factors such as antibody positivity or drug use.

Of particular interest are autoantibodies targeting DNA, particularly since (in animal models and cell cultures) some of these antibodies may penetrate cells and interfere with DNA repair, and so potentially be lethal to cancer cells and hence protect against breast cancer.[13] This may be most important for BRCA2-deficient breast cancers; unfortunately we did not have enough detailed information on pathology (or sufficient power) to study this subset of malignancies, which do not account for the majority of cancers in the general population (or SLE)[14]

Despite strengths, there are several potential limitations to our study. The mean adjusted SLEDAI-2K values in our analyses were usually based on yearly assessments, and thus we may have missed some relevant information on disease activity. In addition, anti-DNA antibodies were measured by different standard techniques at different centres and/or across the course of the study. Enzyme-linked immunosorbent assays were used most frequently, followed by Crithidia and rarely Farr radioimmunoassay. Anti-dsDNA antibody results may be variable between assays. Moreover, the dsDNA antibody test information that we relied on recorded results as positive or negative; thus, we could not assess the effect of antibody titre on breast cancer risk. As well, we did not have information on past mammography screening or estrogen receptor status on the cases.

Potentially most importantly, the strongest current hypothesis concerning the role of anti-dsDNA antibodies in mediating cancer risk in SLE is that the effect may be due only to specific subtypes of antibodies, that is, cell-penetrating autoantibodies, which may represent only a subset of the anti-DNA antibodies found in SLE. This may also explain the lack of an association between anti-DNA antibodies and lowered breast cancer risk. Finally, we did not attempt to assess whether different subtypes of breast cancer are affected preferentially by anti-ds DNA antibodies, or whether the antibodies affected the course of breast cancer. These are all areas of potential interest for future study.

We also did not find a clear association between breast cancer and lupus-related drug exposure. Cyclophosphamide has been suspected of being a trigger for certain malignancies in diseases like SLE,

particularly hematological cancers [9] though it has not been clearly linked to breast cancers. On the other hand antimalarial drugs (commonly used in SLE) have been proposed to have a potential role in lowering cancer risk [15] One hypothesis is that anti-malarial drugs might promote, in cancer cells, a type of cell death process called autophagy. [16-17] Our current analyses do not strongly suggest a protective role for this agent, at least with respect to breast cancer. However, even with our large sample, most of the drug effect estimates were too imprecise to definitively rule out positive or negative effects on breast cancer risk in SLE.

As might be expected (being risk factors for breast cancer in the general population [18]), age was an important risk factor for breast cancer, in unadjusted and adjusted analyses. White race, menopausal status, ever-use of hormone replacement therapy, and family history of breast cancer were associated with breast cancer in univariate analyses, although the associations were less clear in the multivariate analyses. Within the general population, women of different racial/ethnic groups have different breast cancer risk profiles. This likely explains the higher breast cancer rates for white SLE patients in our univariate analysis.

Earlier, we used general population breast cancer genome-wide association study (GWAS) data, to explore whether single nucleotide polymorphisms (SNPs) predisposing to SLE might be protective against breast cancer (in women in the general population) [19]. We focused on loci relevant to 10 SNPs that are highly associated with SLE. The one SLE-related SNP with a potentially protective odds ratio (OR) within the GWAS breast cancer cases versus controls, was the rs9888739-C allele (OR 0.90755, uncorrected p value 0.0499, which is not strongly convincing). Thus if a decreased breast cancer risk in SLE is influenced by genetic profiles, this may be due to other SNPs, complex interactions, and/or epigenetic factors.

In summary, in our study of over 4,000 SLE patients, the principal factors associated with breast cancers were older age at cohort entry. There was little evidence that breast cancer risk in this SLE sample was strongly driven by any of the clinical factors that we studied. Further search for factors that determine the lower risk of breast cancer in SLE is warranted.



**Conflict of interest:**

The authors declare no conflict of interest.

**Acknowledgements:** This work has been funded by the CIHR and NIH. The Johns Hopkins SLE cohort research activities are funded by the NIH AR grant #43727. The Montreal SLE cohort research activities are funded by the Singer Family Fund for Lupus Research. Dr. Bernatsky is the recipient of a senior career award from Fonds de recherche du Québec-Santé. Dr. Fortin is the recipient of a Canada Research Chair. The Northwestern SLE cohort is supported by NIH AR grant # 066464. The Birmingham UK lupus cohort has been supported by Lupus UK and the Birmingham NIHR/Wellcome Trust Clinical Research Facility.

## References

- <sup>1</sup> Bernatsky S, Kale M, Ramsey-Goldman R, Gordon C, Clarke AE. SLE and Malignancies. *Curr Opin Rheumatol*. 2012 Mar;24(2):177-81
- <sup>2</sup> Bernatsky S, Ramsey-Goldman R, Foulkes WD, Gordon C, Clarke AE. Breast, ovarian, and endometrial malignancies in systemic lupus erythematosus: a meta-analysis. *Br J Cancer*. 2011 Apr 26;104(9):1478-81.
- <sup>3</sup> Bernatsky S, Ramsey-Goldman R, Labrecque J, Joseph L, Boivin JF, Petri M, et al Cancer risk in systemic lupus: an updated international multi-centre cohort study. *J Autoimmun*. 2013;42:130-135
- <sup>4</sup> Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus [letter]. *Arthritis Rheum* 1997;40:1725
- <sup>5</sup> Barlow WE, Ichikawa L, Rosner D, Izumi S. Analysis of case-cohort designs. *J Clin Epidemiol*. 1999 Dec;52(12):1165-72
- <sup>6</sup> Ibañez D, Urowitz MB, Gladman DD. Summarizing disease features over time: I. Adjusted mean SLEDAI derivation and application to an index of disease activity in lupus. *J Rheum*. 2003;30:1977-82
- <sup>7</sup> Ibañez D, Gladman DD, Urowitz MB. Adjusted mean Systemic Lupus Erythematosus Disease Activity Index-2K is a predictor of outcome in SLE. *J Rheumatol*. 2005 May;32(5):824-7.
- <sup>8</sup> Yazdany J, Yelin EH, Panopalis P, Trupin L, Julian L, Katz PP. Validation of the systemic lupus erythematosus activity questionnaire in a large observational cohort. *Arthritis Rheum* 2008; 59:136-143.
- <sup>9</sup> Bernatsky S, Joseph L, Boivin JF, Gordon C, Urowitz M, et al. The relationship between cancer and medication exposures in systemic lupus erythematosis: a case-cohort study. *Ann Rheum Dis*. 2008 Jan;67(1):74-9
- <sup>10</sup> Breast Cancer Rates by Race and Ethnicity U.S. Centers for Disease Control and Prevention <http://www.cdc.gov/cancer/breast/statistics/race.htm> Accessed December 2015
- <sup>11</sup> Parikh-Patel A, Allen M, Cress R, White RH. Cancer risk in a cohort of patients with systemic lupus erythematosus (SLE) in California. *Cancer causes & control* 2008;19(8):887-894
- <sup>12</sup> Gadalla SM, Amr S, Langenberg P, Baumgarten M, Davidson WF, Schairer C et al. Breast cancer risk in elderly women with systemic autoimmune rheumatic diseases: a population-based case-control study. *Br J Cancer* 2009; 100(5):817-821.
- <sup>13</sup> Hansen JE, Chan G, Liu Y, Hegan DC, Dalal S, Dray E, Kwon Y, Xu Y, Xu X, Peterson-Roth E, Geiger E, Liu Y, Gera J, Sweasy JB, Sung P, Rockwell S, Nishimura RN, Weisbart RH, Glazer PM. Targeting cancer with a lupus autoantibody. *Sci Transl Med*. 2012 Oct 24;4(157):157ra142
- <sup>14</sup> Tessier Cloutier B, Clarke AE, Ramsey-Goldman R, Wang Y, Foulkes W, Gordon C, Hansen JE, Yelin E, Urowitz MB, Gladman D, Fortin PR, Wallace DJ, Petri M, Manzi S, Ginzler EM, Labrecque J, Edworthy S, Dooley MA, Senécal JL, Peschken CA, Bae SC, Isenberg D, Rahman A, Ruiz-Irastorza G, Hanly JG, Jacobsen S, Nived O, Witte T, Criswell LA, Barr SG, Dreyer L, Sturfelt G, Bernatsky S. Breast cancer in systemic lupus erythematosus. *Oncology*. 2013;85(2):117-21
- <sup>15</sup> Ruiz-Irastorza G, Ugarte A, Egurbide MV, Garmendia M, Pijoan JI, Martinez-Berriotxo A, Aguirre C. Antimalarials may influence the risk of malignancy in systemic lupus erythematosus. *Ann Rheum Dis*. 2007 Jun;66(6):815-7.
- <sup>16</sup> Rahim R, Strobl JS. Hydroxychloroquine, chloroquine, and all-trans retinoic acid regulate growth, survival, and histone acetylation in breast cancer cells. *Anticancer Drugs* 2009; 20(8):736-745.

---

<sup>17</sup> Amaravadi RK. Autophagy-induced tumor dormancy in ovarian cancer. *J Clin Invest* 2008; 118(12):3837-3840.

<sup>18</sup> Keegan TH, Chang ET, John EM, Horn-Ross PL, Wrensch MR, Glaser SL, Clarke CA. Recent changes in breast cancer incidence and risk factor prevalence in San Francisco Bay area and California women: 1988 to 2004. *Breast Cancer Res.* 2007;9(5):R62. doi: 10.1186/bcr1768

<sup>19</sup> Bernatsky S, Easton DF, Dunning A, Michailidou K, Ramsey-Goldman R, Gordon C, Clarke AE, Foulkes W. Decreased breast cancer risk in systemic lupus erythematosus: the search for a genetic basis continues. *Lupus.* 2012;21(8):896-9.